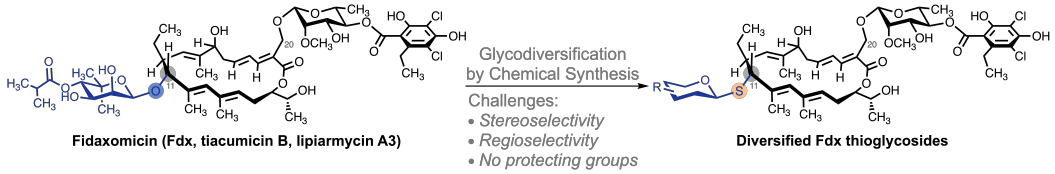
Semi-Synthesis of Thioglycoside Derivatives of the Natural Product Antibiotic Fidaxomicin

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Antibiotic treatments can disturb the gut flora and can give rise to the proliferation of pathogens. The pathogen *Clostridioides difficile* (*C. diff.*) constitutes the most frequent cause of nosocomial infections, and can evoke diarrhea, but in severe cases also lead to sepsis or death.[1,2] The repertoire of treatment options is limited to mainly the antibiotics fidaxomicin, vancomycin, and metronidazole. Out of these, the natural product macrolactone fidaxomicin (Fdx, tiacumicin B, lipiarmycin A3) is the gold-standard treatment due to low recurrence-rates and high selectivity for *C. diff*.[1–4] The limited treatment options along with the potential for resistance development emphasize the need for research on antibiotics targeting *C. diff*. Our aim is to access structural diversification of the Fdx parent compound to slow-down resistance development of *C. diff.* and to optimize the PK/PD profile.

Fdx targets the bacterial RNA polymerase inhibiting the transcription initiation process, culminating in bactericidal activity.[5,6] Structurally, Fdx comprises a core aglycon linked to carbohydrate moieties at the C11- and C20-position. The D-noviose-derived sugar at C11 binds deep within the relatively narrow binding site for Fdx. In this work, we will present our strategy to access glycodiversification at C11 under mild conditions leaving the rest of the molecule intact. In addition, we will discuss how we avoid the use of protecting groups on Fdx, the regio- and stereochemical outcome of these reactions and present the synthetic strategy to access non-classical 1-thio-noviose derivatives. Further, the biochemical characterization of the new Fdx derivatives will be presented.



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